

Appl. No. : 09/847,208
Filed : May 1, 2001

multivalent antigen (allergen) to antigen-specific IgE specifically bound to Fc ϵ RI on the surface of mast cells and basophils stimulates a complex series of signaling events that culminate in the release of host vasoactive and proinflammatory mediators contributing to both acute and late-phase allergic responses (Metcalfe *et al.*, *Physiol. Rev.* 77:1033-1079 (1997)).--

*C /
Correl*
Please delete the paragraph spanning page 2 (line 28) through page 3 (line 9), and replace it with the following substitute paragraph:

CJ
--Along with the stimulatory Fc ϵ RI, mast cells and basophils co-express an immunoreceptor tyrosine-based inhibition motif (ITIM)-containing inhibitory low-affinity receptor, Fc γ RIIb, that acts as a negative regulator of antibody function. Fc γ RIIb represents a growing family of structurally and functionally similar inhibitory receptors, the inhibitory receptor superfamily (IRS), that negatively regulate ITAM-containing immune receptors (Ott and Cambier, *J. Allergy Clin. Immunol.*, 106:429-440 (2000)) and a diverse array of cellular responses. Coaggregation of an IRS member with an activating receptor leads to phosphorylation of the characteristic ITIM tyrosine and subsequent recruitment of the SH2 domain-containing protein tyrosine phosphatases, SHP-1 and SHP-2, and the SH2 domain-containing phospholipases,SHIP and SHIP2 (Cambier, J.C., *Proc. Natl. Acad. Sci. USA*, 94:5993-5995 (1997)). Possible outcomes of the coaggregation include inhibition of cellular activation, as demonstrated by the coaggregation of Fc γ RIIb and B-cell receptors, T-cell receptors, activating receptors, including Fc ϵ RI, or cytokine receptors (Malbec *et al.*, *Curr. Top. Microbiol. Immunol.*, 244:13-27 (1999)).--

C 3
Please delete the paragraph on page 3 consisting of lines 10 through 24, and replace it with the following substitute paragraph:

--Most studies have so far concentrated on elucidating the mechanisms of Fc γ RII, in particular Fc γ RIIb, function. The three alternatively spliced isoforms of the Fc γ IIb receptor, of which Fc γ RIIb1' is only found in mice, and Fc γ RIIb1 and Fc γ RIIb2 are expressed in both humans and mice, have Ig-like loops and a conserved ITIM, but differ in their cytoplasmic domains. Co-crosslinking of the high-affinity Fc ϵ RI receptor and the inhibitory low-affinity receptor Fc γ RII blocks a number of processes, including Fc ϵ RI-mediated secretion, IL-4 production, Ca²⁺ mobilization, Syk phosphorylation, and Fc ϵ RI-mediated basophil and mast cell activation. In B

Appl. No. : 09/847,208
Filed : May 1, 2001

cells, co-crosslinking of the B-cell receptor and Fc γ RIIb inhibits B-cell receptor-mediated cell activation (Cambier, J.C., *Proc. Natl. Acad. Sci.*, 94:5993-5995 (1997); Daeron, M., *Annu. Rev. Immunol.*, 15:203-234 (1997)), and specifically, inhibits B-cell receptor-induced blastogenesis and proliferation (Chan et al., *Immunology*, 21:967-981 (1971); Phillips and Parker, *J. Immunol.*, 132:627-632 (1984)) and stimulates apoptosis (Ashman et al., *J. Immunol.*, 157:5-11 (1996)).
CB
Conne
Coaggregation of Fc γ RIIb1 or Fc γ RIIb2 with Fc ϵ RI in rat basophilic leukemia cells, inhibits Fc ϵ RI-mediated release of serotonin and TNF- α (Daeron et al., *J. Clin. Invest.*, 95:577-85 (1995); Daeron et al., *Immunity*, 3:635-646 (1995)).--

Please delete the paragraph on page 10 consisting of lines 3 through 9, and replace it with the following substitute paragraph:

C4
--The binding is "specific" when the binding affinity of a molecule for a binding target, e.g. an IgG or IgE receptor, is significantly higher (preferably at least about 2-times, more preferably at least about 4-times, most preferably at least about 6-times higher) than the binding affinity of that molecule to any other known native polypeptide.--

Please delete the paragraph on page 10 consisting of lines 13 through 27, and replace it with the following substitute paragraph:

C5
--The terms "receptor comprising an immune receptor tyrosine-based inhibitory motif (ITIM)" and "ITIM-containing receptor" are used to refer to a receptor containing one or more immune receptor tyrosine-based inhibitory motifs, ITIMs. The ITIM motif can be generally represented by the formula Val/Ile-Xaa-PTyr-Xaa-Xaa-Leu/Val (where Xaa represents any amino acid). ITIM-containing receptors include, without limitation, Fc γ RIIb, gp49b1/gp91 (Arm et al., *J. Biol. Chem.* 266:15966-73 (1991)), p91/PIR-B (Hayami et al., *J. Biol. Chem.* 272:7320-7 (1997)), LIR1-3, 5, 8, LAIR-1; CD22 (van Rossenberg et al., *J. Biol. Chem.* 276(16):12967-12973 [2001]); CTL-4, CD5, p58/70/140 KIR, PIRB2-5; NKB1, Ly49 A/C/E/F/G, NKG2-A/B, APC-R, CD66, CD72, PD-1, SHPS-1, SIRP- α 1, IL T1-5, MIR7, 10, hMIR(HM18), hMIR(HM9), Fas(CD95), TGF β -R, TNF-R1, IFN- γ -R (α - and β -chains), mast cell function Ag, H2-M, HLA-DM, CD1, CD1-d, CD46, c-cbl, Pyk2/FADK2, P130 Ca rel prot, PGDF-R, LIF, LIR-R, CIS, SOCS13 and 3, as reviewed in Sinclair NR et al., *supra*. Ligands for many of these receptors are also known, such as, e.g. the ligand for CD95 is called CD95 ligand, the ligands for

Appl. No. : 09/847,208
Filed : May 1, 2001

CTLA-4 are CD80 and CD86, the ligands of IFN- γ receptor is IFN- γ , etc. Ligands for CD22 comprise the basic binding motif Nau5Ac-a(2,6)-Lac, and are discussed, for example in van Rossenberg *et al.*, 2001, *supra*.-

Conc C5
Please delete the paragraph on page 23 consisting of lines 6 through 14, and replace it with the following substitute paragraph:

C 6
--The second polypeptide sequence present in the fusion molecules of the invention preferably has at least about 80%, more preferably at least about 85%, even more preferably at least about 90%, yet more preferably at least about 95%, most preferably at least about 99% sequence identity with the amino acid sequence of the CH2-CH3-CH4 region of a native IgE immunoglobulin, preferably native human IgE, or with the sequence of a native allergen protein. In a particularly preferred embodiment, the sequence identity is defined with reference to the human CH ϵ 2-CH ϵ 3-CH ϵ 4 sequence of SEQ ID NO: 6 or with regard to one of the allergen sequences listed in Table 1 below (SEQ ID NOS: 8 through 173), or, in a preferred embodiment, a peanut allergen, e.g., Ara h1, Ara h2 or Ara h3 (see, SEQ ID NOS: 27-28 and 176-177).--

Please delete TABLE 1 spanning pages 30 through 40, and replace it with the following substitute TABLE 1:

--TABLE 1

Allergen	SWISS-PROT Entry	SWISS-PROT Accession No.	Protein Name	Source	SEQ ID NO.
Aln g 1	MPAG_ALNGL	P38948	Major Pollen Allergen Aln g 1	Pollen of Alnus glutinosa (Alder)	8
Alt a 6	RLA2_ALTAL	P42037	60S Acidic Ribosomal Protein P2	Alternaria alternata	9
Alt a 7	ALA7_ALTAL	P42058	Minor Allergen Alt a 7	Alternaria alternata	10
Alt a 10	DHAL_ALTAL	P42041	Aldehyde Dehydrogenase	Alternaria alternata	11
Alt a 12	RLA1_ALTAL	P49148	60S Acidic Ribosomal Protein P1	Alternaria alternata	12
Amb a 1	MP11_AMBAR	P27759	Pollen Allergen Amb a 1.1 [Precursor]	Ambrosia artemisiifolia (Short ragweed)	13
Amb a 1	MP12_AMBAR	P27760	Pollen Allergen Amb a 1.2 [Precursor]	Ambrosia artemisiifolia (Short ragweed)	14
Amb a 1	MP13_AMBAR	P27761	Pollen Allergen Amb a 1.3 [Precursor]	Ambrosia artemisiifolia (Short ragweed)	15

Appl. No. : 09/847,208
 Filed : May 1, 2001

Allergen	SWISS-PROT Entry	SWISS-PROT Accession No.	Protein Name	Source	SEQ ID NO.
Amb a 1	MP14_AMBAR	P28744	Pollen Allergen Amb a 1.4 [Precursor]	Ambrosia artemisiifolia (Short ragweed)	16
Amb a 2	MPA2_AMBAR	P27762	Pollen Allergen Amb a 2 [Precursor]	Ambrosia artemisiifolia (Short ragweed)	17
Amb a 3	MPA3_AMBEL	P00304	Pollen Allergen Amb a 3	Ambrosia artemisiifolia var. elatior (Short ragweed)	18
Amb a 5	MPA5_AMBEL	P02878	Pollen Allergen Amb a 5	Ambrosia artemisiifolia var. elatior (Short ragweed)	19
Amb p 5	MPA5_AMBPS	P43174	Pollen Allergen Amb p 5-a [Precursor]	Ambrosia psilostachya (Western ragweed)	20
Amb p 5	MP5B_AMBPS	P43175	Pollen Allergen Amb p 5b [Precursor]	Ambrosia psilostachya (Western ragweed)	21
Amb t 5	MPT5_AMBTR	P10414	Pollen Allergen Amb t 5 [Precursor]	Ambrosia trifida (Giant ragweed)	22
Api g 1	MPAG_APIGR	P49372	Major Allergen Api g 1	Apium grayeolens (Celery)	23
Api m 1	PA2_APIME	P00630	Phospholipase A2 [Precursor] [Fragment]	Apis mellifera (Honeybee)	24
Api m 2	HUGA_APIME	Q08169	Hyaluronoglucosaminidase [Precursor]	Apis mellifera (Honeybee)	25
Api m 3	MEL_APIME	P01501	Melittin [Precursor]	Apis mellifera (Honeybee) Apis cerana (Indian honeybee)	26
Ara h 1	AH11_ARAHY	P43237	Allergen Ara h 1, Clone P17	Arachis hypogaea (Peanut)	27
Ara h 1	AH12_ARAHY	P43238	Allergen Ara h 1, Clone P41b	Arachis hypogaea (Peanut)	28
Ara t 8	PRO1_ARATH	Q42449	Profilin 1	Arabidopsis thaliana (Mouse-ear cress)	29
Asp f 1	RNMG_ASPRE	P04389	Ribonuclease Mitogillin [Precursor]	Aspergillus restrictus; Aspergillus fumigatus (Sartorya fumigata)	30
Asp f 2	MAF2_ASFFU	P79017	Major Allergen Asp f 2 [Precursor]	Aspergillus fumigatus (Sartorya fumigata)	31
Asp f 3	PM20_ASFFU	O43099	Probable Peroxisomal Membrane Protein PMP20	Aspergillus fumigatus (Sartorya fumigata)	32
Asp f 13	AF13_ASFFU	O60022	Allergen Asp f 13 [Precursor]	Aspergillus fumigatus (Sartorya fumigata)	33
Bet v 1	BV1A_BETVE	P15494	Major Pollen Allergen Bet v 1-a	Betula verrucosa (White birch) (Betula pendula)	34
Bet v 1	BV1C_BETVE	P43176	Major Pollen Allergen Bet v 1-c	Betula verrucosa (White birch) (Betula pendula)	35
Bet v 1	BV1D_BETVE	P43177	Major Pollen Allergen Bet v 1-d/h	Betula verrucosa (White birch) (Betula pendula)	36

Appl. No. : 09/847,208
 Filed : May 1, 2001

RECEIVED
 FEB 04 2002

TECH CENTER SEQ ID NO. 600/2900

Allergen	SWISS-PROT Entry	SWISS-PROT Accession No.	Protein Name	Source	SEQ ID NO.
Bet v 1	BV1E_BETVE	P43178	Major Pollen Allergen Bet v 1-e	Betula verrucosa (White birch) (<i>Betula pendula</i>)	37
Bet v 1	BV1F_BETVE	P43179	Major Pollen Allergen Bet v 1-f/i	Betula verrucosa (White birch) (<i>Betula pendula</i>)	38
Bet v 1	BV1G_BETVE	P43180	Major Pollen Allergen Bet v 1-g	Betula verrucosa (White birch) (<i>Betula pendula</i>)	39
Bet v 1	BV1J_BETVE	P43183	Major Pollen Allergen Bet v 1-j	Betula verrucosa (White birch) (<i>Betula pendula</i>)	40
Bet v 1	BV1K_BETVE	P43184	Major Pollen Allergen Bet v 1-k	Betula verrucosa (White birch) (<i>Betula pendula</i>)	41
Bet v 1	BV1L_BETVE	P43185	Major Pollen Allergen Bet v 1-l	Betula verrucosa (White birch) (<i>Betula pendula</i>)	42
Bet v 1	BV1M_BETVE	P43186	Major Pollen Allergen Bet v 1-m/n	Betula verrucosa (White birch) (<i>Betula pendula</i>)	43
Bet v 2	PROF-BETVE	P25816	Profilin	Betula verrucosa (White birch) (<i>Betula pendula</i>)	44
Bet v 3	BTB3_BETVE	P43187	Allergen Bet v 3	Betula verrucosa (White birch) (<i>Betula pendula</i>)	45
Bla g 2	ASP2_BLAGE	P54958	Aspartic Protease Bla g 2 [Precursor]	Blattella germanica (German cockroach)	46
Bla g 4	BLG4_BLAGE	P54962	Allergen Bla g 4 [Precursor] [Fragment]	Blattella germanica (German cockroach)	47
Bla g 5	GTS1_BLAGE	O18598	Glutathione-S-transferase	Blattella germanica (German cockroach)	48
Blo t 12	BT12_BLOTA	Q17282	Allergen Blo t 12 [Precursor]	Blomia tropicalis (Mite)	49
Bos d 2	ALL2_BOVIN	Q28133	Allergen Bos d 2 [Precursor]	Bos taurus (Bovine)	50
Bos d 5	LACB_BOVIN	P02754	Beta-lactoglobulin [Precursor]	Bos taurus (Bovine)	51
Bra j 1	ALL1_BRAJU	P80207	Allergen Bra j 1-e, Small and Large Chains	Brassica juncea (Leaf mustard) (Indian mustard)	52
Can a 1	ADH1_CANAL	P43067	Alcohol Dehydrogenase 1	Candida albicans (Yeast)	53
Can f 1	ALL1_CANFA	O18873	Major Allergen Can f 1 [Precursor]	Canis familiaris (Dog)	54
Can f 2	ALL2_CANFA	O18874	Minor Allergen Can f 2 [Precursor]	Canis familiaris (Dog)	55
Car b 1	MPA1_CARBE	P38949	Major Pollen Allergen Car b 1, Isoforms 1A and 1B	Carpinus betulus (Hornbeam)	56
Car b 1	MPA2_CARBE	P38950	Major Pollen Allergen Car b 1, Isoform 2	Carpinus betulus (Hornbeam)	57
Cha o 1	MPA1_CHAOB	Q96385	Major Pollen Allergen Cha o 1 [Precursor]	Chamaecyparis obtusa (Japanese cypress)	58

Appl. No. : 09/847,208
 Filed : May 1, 2001

Allergen	SWISS-PROT Entry	SWISS-PROT Accession No.	Protein Name	Source	SEQ ID NO.
Cla h 3	DHAL_CLAHE	P40108	Aldehyde Dehydrogenase	Cladosporium herbarum	59
Cla h 3	RLA3_CLAHE	P42038	60S Acidic Ribosomal Protein P2	Cladosporium herbarum	60
Cla h 4	HS70_CLAHE	P40918	Heat Shock 70 KDa Protein	Cladosporium herbarum	61
Cla h 4	RLA4_CLAHE	P42039	60S Acidic Ribosomal Protein P2	Cladosporium herbarum	62
Cla h 5	CLH5_CLAHE	P42059	Minor Allergen Cla h 5	Cladosporium herbarum	63
Cla h 6	ENO_CLAHE	P42040	Enolase	Cladosporium herbarum	64
Cla h 12	RLA1_CLAHE	P50344	60S Acidic Ribosomal Protein P1	Cladosporium herbarum	65
Cop c 2	THIO_CAPCM				
Cor a 1	MPAA_CORA V	Q08407	Major Pollen Allergen Cor a 1, Isoforms 5, 6, 11 and 16	Corylus avellana (European hazel)	66
Cup a 1	MPA1_CUPAR	Q9SCG9	Major Pollen Allergen Cup a 1	Cupressus arizonica	67
Cry j 1	SBP_CRYJA	P18632	Sugi Basic Protein [Precursor]	Cryptomeria japonica (Japanese cedar)	68
Cry j 2	MPA2_CRYJA	P43212	Possible Polygalacturonase	Cryptomeria japonica (Japanese cedar)	69
Cyn d 12	PROF_CYNDA	O04725	Profilin	Cynodon dactylon (Bermuda grass)	70
Dac g 2	MPG2_DACGL	Q41183	Pollen Allergen Dac g 2 [Fragment]	Dactylis glomerata (Orchard grass) (Cocksfoot grass)	71
Dau c 1	DAU1_DAUCA	O04298	Major Allergen Dau c 1	Daucus carota (Carrot)	72
Der f 1	MMAL_DERFA A	P16311	Major Mite Fecal Allergen Der f 1 [Precursor]	Dermatophagoides farinae (House-dust mite)	73
Der f 2	DEF2_DERFA	Q00855	Mite Allergen Der f 2 [Precursor]	Dermatophagoides farinae (House-dust mite)	74
Der f 3	DEF3_DERFA	P49275	Mite Allergen Der f 3 [Precursor]	Dermatophagoides farinae (House-dust mite)	75
Der f 6	DEF6_DERFA	P49276	Mite Allergen Der f 6 [Fragment]	Dermatophagoides farinae (House-dust mite)	76
Der f 7	DEF7_DERFA	Q26456	Mite Allergen Der f 7 [Precursor]	Dermatophagoides farinae (House-dust mite)	77
Der m 1	MMAL_DERM I	P16312	Major Mite Fecal Allergen Der m 1 [Fragment]	Dermatophagoides microceras (House-dust mite)	78

Appl. No. : 09/847,208
 Filed : May 1, 2001

RECEIVED
 FEB 04 2002

TECH CENTER
 SP 800/2900
 ID NO.

Allergen	SWISS-PROT Entry	SWISS-PROT Accession No.	Protein Name	Source	SP 800/2900 ID NO.
Der p 1	MMAL_DERPT	P08176	Major Mite Fecal Allergen Der p 1 [Precursor]	Dermatophagoides pteronyssinus (House-dust mite)	79
Der p 2	DER2_DERPT	P49278	Mite Allergen Der p 2 [Precursor]	Dermatophagoides pteronyssinus (House-dust mite)	80
Der p 3	DER3_DERPT	P39675	Mite Allergen Der p 3 [Precursor]	Dermatophagoides pteronyssinus (House-dust mite)	81
Der p 4	AMY_DERPT	P49274	Alpha-Amylase [Fragment]	Dermatophagoides pteronyssinus (House-dust mite)	82
Der p 5	DER5_DERPT	P14004	Mite Allergen Der p 5	Dermatophagoides pteronyssinus (House-dust mite)	83
Der p 6	DER6_DERPT	P49277	Mite Allergen Der p 6 [Fragment]	Dermatophagoides pteronyssinus (House-dust mite)	84
Der p 7	DER7_DERPT	P49273	Mite Allergen Der p 7 [Precursor]	Dermatophagoides pteronyssinus (House-dust mite)	85
Dol a 5	VA5_DOLAR	Q05108	Venom Allergen 5	Dolichovespula arenaria (Yellow hornet)	86
Dol m 1	PA11_DOLMA	Q06478	Phospholipase A1 1 [Precursor] [Fragment]	Dolichovespula maculata (White-face hornet) (Bald-faced hornet)	87
Dol m 1	PA12_DOLMA	P53357	Phospholipase A1 2	Dolichovespula maculata (White-face hornet) (Bald-faced hornet)	88
Dol m 2	HUGA_DOLMA	P49371	Hyaluronoglucosaminidase	Dolichovespula maculata (White-face hornet) (Bald-faced hornet)	89
Dol m 5	VA52_DOLMA	P10736	Venom Allergen 5.01 [Precursor]	Dolichovespula maculata (White-face hornet) (Bald-faced hornet)	90
Dol m 5	VA53_DOLMA	P10737	Venom Allergen 5.02 [Precursor] [Fragment]	Dolichovespula maculata (White-face hornet) (Bald-faced hornet)	91
Equ c 1	ALL1_HORSE	Q95182	Major Allergen Equ c 1 [Precursor]	Equus caballus (Horse)	92
Equ c 2	AL21_HORSE	P81216	Dander major Allergen Equ c 2.0101 [Fragment]	Equus caballus (Horse)	93

Appl. No. : 09/847,208
 Filed : May 1, 2001

Allergen	SWISS-PROT Entry	SWISS-PROT Accession No.	Protein Name	Source	SEQ ID NO.
Equ c 2	AL22_HORSE	P81217	Dander Major Allergen Equ c 2.0102 [Fragment]	Equus caballus (Horse)	94
Eur m 1	EUM1_EURM A	P25780	Mite Group I Allergen Eur m 1 [Fragment]	Euroglyphus maynei (House-dust mite)	95
Fel d 1	FELA_FELCA	P30438	Major Allergen I Polypeptide Chain 1 Major Form [Precursor]	Felis silvestris catus (Cat)	96
Fel d 1	FELB_FELCA	P30439	Major Allergen I Polypeptide Chain 1 Minor Form [Precursor]	Felis silvestris catus (Cat)	97
Fel d 1	FEL2_FELCA	P30440	Major Allergen I Polypeptide Chain 2 [Precursor]	Felis silvestris catus (Cat)	98
Gad c 1	PRVB_GADCA	P02622	Parvalbumin Beta	Gadus callarias (Baltic cod)	99
Gal d 1	IOVO_CHICK	P01005	Ovomucoid [Precursor]	Gallus gallus (Chicken)	100
Gal d 2	OVAL_CHICK	P01012	Ovalbumin	Gallus gallus (Chicken)	101
Gal d 3	TRFE_CHICK	P02789	Ovotransferrin [Precursor]	Gallus gallus (Chicken)	102
Gal d 4	LYC_CHICK	P00698	Lysozyme C [Precursor]	Gallus gallus (Chicken)	103
Hel a 2	PROF_HELAN	O81982	Profilin	Helianthus annuus (Common sunflower)	104
Hev b 1	REF_HEVBR	P15252	Rubber Elongation Factor Protein	Hevea brasiliensis (Para rubber tree)	105
Hev b 5	HEV5_HEVBR	Q39967	Major Latex Allergen Hev b 5	Hevea brasiliensis (Para rubber tree)	106
Hol l 1	MPH1_HOLLA	P43216	Major Pollen Allergen Hol l 1 [Precursor]	Holcus lanatus (Velvet grass)	107
Hor v 1	IAA1_HORVU	P16968	Alpha-amylase Inhibitor Bmai-1 [Precursor] [Fragment]	Hordeum vulgare (Barley)	108
Jun a 1	MPA1_JUNAS	P81294	Major Pollen Allergen Jun a 1 [Precursor]	Juniperus ashei (Ozark white cedar)	109
Jun a 3	PRR3_JUNAS	P81295	Pathogenesis-Related Protein [Precursor]	Juniperus ashei (Ozark white cedar)	110
Lep d 1	LEP1_LEPDS	P80384	Mite Allergen Lep d 1 [Precursor]	Lepidoglyphus destructor (Storage mite)	111
Lol p 1	MPL1_LOLPR	P14946	Pollen Allergen Lol p 1 [Precursor]	Lolium perenne (Perennial ryegrass)	112
Lol p 2	MPL2_LOLPR	P14947	Pollen Allergen Lol p 2-a	Lolium perenne (Perennial ryegrass)	113
Lol p 3	MPL3_LOLPR	P14948	Pollen Allergen Lol p 3	Lolium perenne (Perennial ryegrass)	114

Appl. No. : 09/847,208
 Filed : May 1, 2001

RECEIVED
FEB 04 2002
TECH CENTER
6500/2900

Allergen	SWISS-PROT Entry	SWISS-PROT Accession No.	Protein Name	Source	6500/2900 ID NO.
Lol p 5	MP5A_LOLPR	Q40240	Major Pollen Allergen Lol p 5a [Precursor]	Lolium perenne (Perennial ryegrass)	115
Lol p 5	MP5B_LOLPR	Q40237	Major Pollen Allergen Lol p 5b [Precursor]	Lolium perenne (Perennial ryegrass)	116
Mal d 1	MAL1_MALDO	P43211	Major Allergen Mal d 1	Malus domestica (Apple) (Malus sylvestris)	117
Mer a 1	PROF_MERAN	O49894	Profilin	Mercurialis annua (Annual mercury)	118
Met e 1	TPM1_METEN	Q25456	Tropomyosin	Metapenaeus ensis (Greasyback shrimp) (Sand shrimp)	119
Mus m 1	MUP6_MOUSE	P02762	Major Urinary Protein 6 [Precursor]	Mus musculus (Mouse)	120
Myr p 1	MYR1_MYRPI	Q07932	Major Allergen Myr p 1 [Precursor]	Myrmecia pilosula (Bulldog ant) (Australian jumper ant)	121
Myr p 2	MYR2_MYRPI	Q26464	Allergen Myr p 2 [Precursor]	Myrmecia pilosula (Bulldog ant) (Australian jumper ant)	122
Ole e 1	ALL1_OLEEU	P19963	Major Pollen Allergen	Olea europaea (Common olive)	123
Ole e 4	ALL4_OLEEU	P80741	Major Pollen Allergen Ole e 4 [Fragments]	Olea europaea (Common olive)	124
Ole e 5	SODC_OLEEU	P80740	Superoxide Dismutase [CU-ZN] [Fragment]	Olea europaea (Common olive)	125
Ole e 7	ALL7_OLEEU	P81430	Pollen Allergen Ole e 7 [Fragment]	Olea europaea (Common olive)	126
Ory s 1	MPO1_ORYSA	Q40638	Major Pollen Allergen Ory s 1 [Precursor]	Oryza sativa (Rice)	127
Par j 1	NL11_PARJU	P43217	Probable Nonspecific Lipid-Transfer Protein [Fragment]	Parietaria judaica	128
Par j 1	NL12_PARJU	O04404	Probable Nonspecific Lipid-Transfer Protein 1 [Precursor]	Parietaria judaica	129
Par j 1	NL13_PARJU	Q40905	Probable Nonspecific Lipid-Transfer Protein 1 [Precursor]	Parietaria judaica	130
Par j 2	NL21_PARJU	P55958	Probable Nonspecific Lipid-Transfer Protein 2 [Precursor]	Parietaria judaica	131
Par j 2	NL22_PARJU	O04403	Probable Nonspecific Lipid-Transfer Protein 2 [Precursor]	Parietaria judaica	132
Pha a 1	MPA1_PHAAQ	Q41260	Major Pollen Allergen Pha a 1 [Precursor]	Phalaris aquatica (Canary grass)	133

C1

Appl. No. : 09/847,208
 Filed : May 1, 2001

RECEIVED
 FEB 04 2002
 TECH CENTER 1600/2000

Allergen	SWISS-PROT Entry	SWISS-PROT Accession No.	Protein Name	Source	SEQ ID NO.
Pha a 5	MP51_PHAAQ	P56164	Major Pollen Allergen Pha a 5.1 [Precursor]	Phalaris aquatica (Canary grass)	134
Pha a 5	MP52_PHAAQ	P56165	Major Pollen Allergen Pha a 5.2 [Precursor]	Phalaris aquatica (Canary grass)	135
Pha a 5	MP53_PHAAQ	P56166	Major Pollen Allergen Pha a 5.3 [Precursor]	Phalaris aquatica (Canary grass)	136
Pha a 5	MP54_PHAAQ	P56167	Major Pollen Allergen Pha a 5.4 [Fragment]	Phalaris aquatica (Canary grass)	137
Phl p 1	MPP1_PHLPR	P43213	Pollen Allergen Phl p 1 [Precursor]	Phleum pratense (Common timothy)	138
Phl p 2	MPP2_PHLPR	P43214	Pollen Allergen Phl p 2 [Precursor]	Phleum pratense (Common timothy)	139
Phl p 5	MP5A_PHLPR	Q40962	Pollen Allergen Phl p 5a [Fragment]	Phleum pratense (Common timothy)	140
Phl p 5	MP5B_PHLPR	Q40963	Pollen Allergen Phl p 5b [Precursor] [Fragment]	Phleum pratense (Common timothy)	141
Phl p 6	MPP6_PHLPR	P43215	Pollen Allergen Phl p 6 [Precursor]	Phleum pratense (Common timothy)	142
Phl p 11	PRO1_PHLPR	P35079	Profilin 1	Phleum pratense (Common timothy)	143
Phl p 11	PRO2_PHLPR	O24650	Profilin 2/4	Phleum pratense (Common timothy)	144
Phl p 11	PRO3_PHLPR	O24282	Profilin 3	Phleum pratense (Common timothy)	145
Poa p 9	MP91_POAPR	P22284	Pollen Allergen Kbg 31 [Precursor]	Poa pratensis (Kentucky bluegrass)	146
Poa p 9	MP92_POAPR	P22285	Pollen Allergen Kbg 41 [Precursor]	Poa pratensis (Kentucky bluegrass)	147
Poa p 9	MP93_POAPR	P22286	Pollen Allergen Kbg 60 [Precursor]	Poa pratensis (Kentucky bluegrass)	148
Pol a 5	VA5_POLAN	Q05109	Venom Allergen 5 [Precursor] [Fragment]	Polistes annularis (Paper wasp)	149
Pol d 5	VA5_POLDO	P81656	Venom Allergen 5	Polistes dominulus (European paper wasp)	150
Pol e 5	VA5_POLEX	P35759	Venom Allergen 5	Polistes exclamans (Paper wasp)	151
Pol f 5	VA5_POLFU	P35780	Venom Allergen 5	Polistes fuscatus (Paper wasp)	152
Pru a 1	PRU1_PRUAV	O24248	Major Allergen Pru a 1	Prunus avium (Cherry)	153
Rat n 1	MUP_RAT	P02761	Major Urinary Protein [Precursor]	Rattus norvegicus (Rat)	154
Sol i 2	VA2_SOLIN	P35775	Venom Allergen II [Precursor]	Solenopsis invicta (Red imported fire ant)	155
Sol i 3	VA3_SOLIN	P35778	Venom Allergen III	Solenopsis invicta (Red imported fire ant)	156

Appl. No. : 09/847,208
 Filed : May 1, 2001

Allergen	SWISS-PROT Entry	SWISS-PROT Accession No.	Protein Name	Source	SEQ ID NO.
Sol i 4	VA4_SOLIN	P35777	Venom Allergen IV	Solenopsis invicta (Red imported fire ant)	157
Sol r 2	VA2_SOLRI	P35776	Venom Allergen II	Solenopsis richteri (Black imported fire ant)	158
Sol r 3	VA3_SOLRI	P35779	Venom Allergen III	Solenopsis richteri (Black imported fire ant)	159
Ves c 5	VA51_VESCR	P35781	Venom Allergen 5.01	Vespa crabro (European hornet)	160
Ves c 5	VA52_VESCR	P35782	Venom Allergen 5.02	Vespa crabro (European hornet)	161
Ves f 5	VA5_VESFL	P35783	Venom Allergen 5	Vespula flavopilosa (Yellow jacket) (Wasp)	162
Ves g 5	VA5_VESGE	P35784	Venom Allergen 5	Vespula germanica (Yellow jacket) (Wasp)	163
Ves m 1	PA1_VESMC	P51528	Phospholipase A1	Vespula maculifrons (Eastern yellow jacket) (Wasp)	164
Ves m 5	VA5_VESMC	P35760	Venom Allergen 5	Vespula maculifrons (Eastern yellow jacket) (Wasp)	165
Ves p 5	VA5_VESPE	P35785	Venom Allergen 5	Vespula pensylvanica (Western yellow jacket) (Wasp)	166
Ves s 5	VA5_VESSQ	P35786	Venom Allergen 5	Vespula squamosa (Southern yellow jacket) (Wasp)	167
Ves v 1	PA1_VESVU	P49369	Phospholipase A1 [Precursor]	Vespula vulgaris (Yellow jacket) (Wasp)	168
Ves v 2	HUGA_VESVU	P49370	Hyaluronoglucosaminidase	Vespula vulgaris (Yellow jacket) (Wasp)	169
Ves v 5	VA5_VESVU	Q05110	Venom Allergen 5 [Precursor]	Vespula vulgaris (Yellow jacket) (Wasp)	170
Ves vi 5	VA5_VESVI	P35787	Venom Allergen 5	Vespula vidua (Yellow jacket) (Wasp)	171
Vesp m 5	VA5_VESMA	P81657	Venom Allergen 5	Vespa mandarinia (Hornet)	172
Zea m 1	MPZ1_MAIZE	Q07154	Pollen Allergen Zea m 1	Zea mays (Maize)	173

Please delete the paragraph on page 41 consisting of lines 12 through 25, and replace it with the following substitute paragraph:

--Host cells can be any eukaryotic or prokaryotic hosts known for expression of heterologous proteins. Accordingly, the polypeptides of the present invention can be expressed

Appl. No. : 09/847,208
Filed : May 1, 2001

in eukaryotic hosts, such as eukaryotic microbes (yeast) or cells isolated from multicellular organisms (mammalian cell cultures), plants and insect cells. Examples of mammalian cell lines suitable for the expression of heterologous polypeptides include monkey kidney CV1 cell line transformed by SV40 (COS-7, ATCC CRL 1651); human embryonic kidney cell line 293S (Graham *et al.*, J. Gen. Virol. 36:59 [1977]); baby hamster kidney cells (BHK, ATCC CCL 10); Chinese hamster ovary (CHO) cells (Urlaub and Chasin, Proc. Natl. Acad. Sci. USA 77:4216 [1980]; monkey kidney cells (CVI-76, ATCC CCL 70); African green monkey cells (VERO-76, ATCC CRL-1587); human cervical carcinoma cells (HELA, ATCC CCL 2); canine kidney cells (MDCK, ATCC CCL 34); human lung cells (W138, ATCC CCL 75); and human liver cells (Hep G2, HB 8065). In general myeloma cells, in particular those not producing any endogenous antibody, e.g. the non-immunoglobulin producing myeloma cell line SP2/0, are preferred for the production of the fusion molecules herein.

Cancel
CJ

Please delete the paragraph on page 43 consisting of lines 10 through 23, and replace it with the following substitute paragraph:

C9
--In certain instances, especially if the two polypeptide sequences making up the bifunctional molecule of the present invention are connected with a non-polypeptide linker, it may be advantageous to individually synthesize the first and second polypeptide sequences, e.g. by any of the recombinant approaches discussed above, followed by functionally linking the two sequences.--

Please delete the paragraph spanning page 43 (line 24) through page 44 (line 10), and replace it with the following substitute paragraph:

C 10
--The fusion molecules of the present invention may include amino acid sequence variants of native immunoglobulin (e.g. IgG and/or IgE) or allergen (e.g., Ara h 2 sequences). Such amino acid sequence variants can be produced by expressing the underlying DNA sequence in a suitable recombinant host cell, or by *in vitro* synthesis of the desired polypeptide, as discussed above. The nucleic acid sequence encoding a polypeptide variant is preferably prepared by site-directed mutagenesis of the nucleic acid sequence encoding the corresponding native (e.g. human) polypeptide. Particularly preferred is site-directed mutagenesis using polymerase chain reaction (PCR) amplification (see, for example, U.S. Pat. No. 4,683,195 issued

Appl. No. : 09/847,208
Filed : May 1, 2001

28 July 1987; and Current Protocols In Molecular Biology, Chapter 15 (Ausubel *et al.*, ed., 1991). Other site-directed mutagenesis techniques are also well known in the art and are described, for example, in the following publications: Current Protocols In Molecular Biology, *supra*, Chapter 8; Molecular Cloning: A Laboratory Manual, 2nd edition (Sambrook *et al.*, 1989); Zoller *et al.*, Methods Enzymol. 100:468-500 (1983); Zoller & Smith, DNA 3:479-488 (1984); Zoller *et al.*, Nucl. Acids Res., 10:6487 (1987); Brake *et al.*, Proc. Natl. Acad. Sci. USA 81:4642-4646 (1984); Botstein *et al.*, Science 229:1193 (1985); Kunkel *et al.*, Methods Enzymol. 154:367-82 (1987), Adelman *et al.*, DNA 2:183 (1983); and Carter *et al.*, Nucl. Acids Res., 13:4331 (1986). Cassette mutagenesis (Wells *et al.*, Gene, 34:315 [1985]), and restriction selection mutagenesis (Wells *et al.*, Philos. Trans. R. Soc. London SerA, 317:415 [1986]) may also be used.--

Please delete the paragraph on page 46 consisting of lines 6 through 12, and replace it with the following substitute paragraph:

--*Uses of compounds for targeted diseases* The compounds disclosed herein can be used to inhibit acute or chronic IgE mediated reactions to major environmental and occupational allergens, can be used to provide for allergy vaccination (immunotherapy) to induce a state of non-allergic reactivity to specific allergens and can also have a prophylactic effect against allergic disease by preventing allergic sensitization to environmental and occupational allergens when administered to at-risk individuals (e.g., those at genetic risk of asthma and those exposed to occupational allergens in the workplace).--

Please delete the paragraph spanning page 46 (line 23) through page 47 (line 8), and replace it with the following substitute paragraph:

--The present invention of gamma allergen bifunctional fusion molecules provides for a novel form of allergy vaccination that will be safer and more effective in the treatment of a variety of IgE mediated allergic reactivity, including, without limitation, asthma, allergic rhinitis, atopic dermatitis, food allergies, urticaria and angioedema, up to and including anaphylactic shock. Having the allergen fused to a molecule that will bind to Fc γ RIIb on mast cells and basophils will prevent the allergen being able to induce local or systemic allergic reactions. Such local or systemic allergic reactions are major problem in allergen vaccination as currently

Appl. No. : 09/847,208
Filed : May 1, 2001

practiced. The gamma-allergen fusion proteins will be able to be given in higher doses over a shorter interval and with greater safety than standard allergen therapy. In addition, use of the gamma-allergen compounds will cause antigen specific desensitization to that specific allergen. Thus the gamma-allergen compounds will give a window of safe exposure to the allergen be it as an acute or recurring treatment as would be needed in using a therapeutic monoclonal antibody to which a patient has developed an allergic (IgE) response or as chronic treatment for prevention of unintentional exposures such as occurs with peanut allergens. This use is expected to gain added importance, as the number of recombinant biological products entering the clinical arena will be increasing dramatically in the near future. The gamma-allergen compounds can even be used along with conventional allergen vaccination so as to provide an extra margin of safety while large doses of standard allergen are given.--

Please delete the paragraph on page 47 consisting of lines 9 through 28, and replace it with the following substitute paragraph:

--In addition, the chimeric gamma-epsilon compounds herein hold great promise for the treatment of chronic urticaria and angioedema. Urticaria is a skin symptom that may accompany allergies but often is idiopathic. It is a relatively common disorder caused by localized cutaneous mast cell degranulation, with resultant increased dermal vascular permeability culminating in pruritic wheals. Angioedema is a vascular reaction involving the deep dermis or subcutaneous or submucosal tissues caused by localized mast cell degranulation. This results in tissue swelling that is pruritic or painful. Chronic urticaria and angioedema often occur together although they occur individually as well. These conditions are common and once present for more than six months, they often last a decade or more. Although not fatal, they are very troubling to patients, as the frequent recurring attacks disrupt daily activities and thereby result in significant morbidity. Standard therapy is often unsuccessful in treating these conditions, which are distressing to the point that chemotherapy with cyclosporine and other potent immunosuppressive drugs has recently been advocated. Increasing evidence suggests that as many as 60% of patients with these conditions actually have an autoimmune disease, in which they make functional antibodies against the Fc ϵ RI receptor. For further details, see Hide *et al.*, *N. Engl. J. Med.* 328:1599-1604 (1993); Fiebiger *et al.*, *J. Clin. Invest.* 96:2606-12 (1995); Fiebiger *et al.*, *J. Clin. Invest.* 101:243-51 (1998); Kaplan, A.P., Urticaria and Angioedema, In:

Appl. No. : 09/847,208
Filed : May 1, 2001

COPY
Inflammation: Basic Principles and Clinical Correlates (Galliin and Snyderman eds.), 3rd Edition, Lippincott & Wilkins, Philadelphia, 1999, pp. 915-928. The fusion molecules of the present invention are believed to form the basis for a novel and effective treatment of these diseases by safely blocking access to the Fc ϵ RI.--

Please delete the paragraph spanning page 52 (line 27) through page 53 (line 2), and replace it with the following substitute paragraph:

C 13
--*Expression and Purification* - The expression vector containing chimeric Fc γ -Fc ϵ gene was linearized at the PvuI site and transfected into SP2/0 cells by electroporation (Bio-Rad). Stable transfectants were selected for growth in medium containing 1 mg/ml geneticine. Clones producing the fusion protein were identified by ELISA using plates coating anti-human IgE (CIA7.12) or IgG (Sigma) antibody. Supernatants from clones were added to wells, and bound protein was detected using goat anti-human IgE or IgG conjugated to alkaline phosphatase (KPL). The fusion protein was purified from the supernatants and ascites by using rProtein A column (Pharmacia).--

C 14
Please delete the paragraph on page 53 consisting of lines 3 through 7, and replace it with the following substitute paragraph:

--*Western Blotting* - The purified protein was run on 7.5% SDS polyacrylamide gel. After transfer, the nylon membrane was blocked by 4% bovine serum albumin/PBS/Tween overnight at 4 °C. For protein detection, the blot was probed with either goat anti-human IgE (ϵ chain specific) or goat anti-human IgG (γ chain-specific) conjugated to alkaline phosphatase (KPL). Color development was performed with an alkaline phosphatase conjugated substrate kit (Bio-Rad).

Please enter the attached substitute Sequence Listing to replace the Sequence Listing currently on file.

IN THE CLAIMS:

Please amend claims 40 and 41 to read as follows: